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10/070,882	03/11/2002	Richard William Titball	41577/270459	2737
7590	03/23/2005		EXAMINER	
John S Pratt Kilpatrick Stockton Suite 2800 1100 Peachtree Street Atlanta, GA 30309-4530			DEVI, SARVAMANGALA J N	
			ART UNIT	PAPER NUMBER
			1645	
DATE MAILED: 03/23/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/070,882	TITBALL ET AL.
	Examiner	Art Unit
	S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 24 January 2005.  
 2a) This action is FINAL.                            2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-4, 7-15 and 17-22 is/are pending in the application.  
 4a) Of the above claim(s) 1-4, 7-15 and 17-22 (in part) is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-4, 7-15 and 17-22 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 14 October 2003 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
 Paper No(s)/Mail Date 061102.

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_\_.  
 5) Notice of Informal Patent Application (PTO-152)  
 6) Other: \_\_\_\_\_.

## DETAILED ACTION

### Preliminary Amendments

1) Acknowledgment is made of Applicants' amendment filed 03/11/02, 10/14/03 and 1/24/05. With these, Applicants have amended the specification, claims and drawing(s).

### Election

2) Acknowledgment is made of Applicants' election filed 11/01/04 of invention I, claims 1-4, 7-15 and 17-22, drawn to a method of enhancing expression of a protein under the control of *PphoP* promoter (SEQ ID NO: 2) and a recombinant gut-colonizing transformed with a construct comprising the promoter, in response to the written lack of unity mailed 09/29/04. Applicants have elected with traverse. Applicants' traversal is on the grounds that inventions I and II share significant commonality in method steps and the end result and therefore are the embodiments of the same inventive concept.

Applicants' argument has been carefully considered, but is not persuasive. As set forth in the written lack of unity mailed 09/29/04, the different promoters used in the methods of different inventions do not share significant structure with each other. Each promoter sequence requires a separate non-coextensive search. For this reason, the lack of unity held in the instant application is proper and hereby made FINAL.

### Status of Claims

3) Claims 5, 6 and 16 have been canceled via the preliminary amendment filed 03/11/02. Claims 2-4 and 7-15 have been amended via the preliminary amendment filed 03/11/02. New claims 17-22 have been added via the preliminary amendment filed 03/11/02. Claims 3, 11, 21 and 22 have been amended via the preliminary amendment filed 01/24/05. Claims 1-4, 7-15 and 17-22 are pending. Claims 1-4, 7-15 and 17-22, with regard to the inclusion of the promoter *OmpC* or *pagC*, have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1-4, 7-15 and 17-22 are under examination. A First Action on the Merits is issued for these claims.

### **Sequence Listing**

**4)** The raw sequence listing submitted in this application has been entered on 10/21/2003.

### **Information Disclosure Statement**

**5)** Acknowledgment is made of Applicant's Information Disclosure Statement filed 06/11/02. The information referred to therein has been considered and a signed copy is attached to this Office Action.

### **Priority**

**6)** The instant application is a national stage 371 application of the international application PCT/GB00/03402 filed 09/06/00 and claims foreign priority to applications 0017000.1 filed 07/12/00 and 9921275.5 filed 09/10/1999 in the United Kingdom

It is noted that Applicants have filed certified copies of the foreign priority to applications 03/11/2002.

### **Specification - Informalities**

**7)** The specification of the instant application is objected to for the following reasons:

(A) To be consistent with the drawings for Figures 3a and 3b and Figures 7a and 7b, on page 12 of the instant specification, Applicants should refer to 'Figure 3' and 'Figure 7' in lines 16 and 33 respectively as --Figures 3a and 3b-- and --Figures 7a and 7b-- respectively.

(B) The use of the trademark in the instant specification has been noted. For example, see line 18 of page 19: 'tween 20'. The recitation should be capitalized wherever they appear or be accompanied by the generic terminology. See M.P.E.P 608.01(V) and Appendix 1. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to trademark recitations, wherever such recitations appear.

(C) The instant application is informal in the format or arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicants' use.

Content of Specification

- (a) Title of the Invention: See 37 C.F.R 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.
- (b) Cross-References to Related Applications: See 37 C.F.R 1.78 and M.P.E.P § 201.11.
- (c) Statement Regarding Federally Sponsored Research and Development: See M.P.E.P § 310.
- (d) Reference to a "Microfiche Appendix": See 37 C.F.R 1.96(c) and M.P.E.P § 608.05. The total number of microfiche and the total number frames should be specified.
- (e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:
  - (1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."
  - (2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."
- (f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 C.F.R 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in

the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

- (g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 C.F.R 1.74.
- (h) Detailed Description of the Invention: A description of the preferred embodiment(s) of the invention as required in 37 C.F.R 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.
- (i) Claim or Claims: See 37 C.F.R 1.75 and M.P.E.P § 608.01(m). The claim or claims must commence on separate sheet. (37 C.F.R 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.
- (j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less on a separate sheet following the claims.
- (k) Drawings: See 37 C.F.R 1.81, 1.83-1.85, and M.P.E.P § 608.02.
- (l) Sequence Listing: See 37 C.F.R 1.821-1.825.

### **Rejection(s) under 35 U.S.C. § 112, First Paragraph (Written Description)**

**8)** Claims 1, 2, 11, 15, 22 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The limitation ‘fragment’ or ‘variant’ as recited in the instant claims 1 and 2, and the limitation ‘antigenic … variant’ as recited in claims 11 and 22 do not exist independent of their functions. The former is required to have  $P_{phoP}$  promoter activity and the latter is required to have the antigenic function. The specification discloses prophylactic application or vaccine intentions for the claimed construct that comprises the recited fragment or variant or that encodes the recited antigenic variant. Prophylactic or vaccine applications minimally require a specific immunogenic and protective action for the ‘antigenic variant’, and the promoter ‘fragment’ or ‘fragments’ and ‘variant’ or ‘variants’ minimally require sufficient promoter activity. The precise structure or relevant identifying characteristics of a representative number of promoter ‘fragments’ or promoter ‘variants’ and a representative number of F1 antigenic ‘variants’ having the above-cited functional activities can only be determined empirically by actually making such ‘variants’ or ‘fragments’, and testing them having the particularly disclosed biological activities. The *Written Description Guidelines* state:

There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement in the specification that the invention includes the use of such a promoter ‘variant’ or promoter ‘fragment’, or an F1 ‘variant’ in the claimed product or method is insufficient to meet the adequate written description requirement of the claimed invention. The promoter ‘variant’ or promoter ‘fragment’, or an F1 ‘variant’, has specific functional or biologic properties dictated by the structure of the ‘variant’ and the ‘fragment’. A convincing structure-function relationship has to exist between the structure of the promoter ‘variant’ or promoter ‘fragment’, and

an ‘antigenic variant’ and the function(s) of the ‘variant’ or ‘fragment’. The function of a promoter ‘variant’ or promoter ‘fragment’ or an F1 ‘variant’ cannot be predicted from the modification of the structure of the  $P_{phoP}$  promoter, or the F1 ‘variant’. Applicants have not shown that variation of a reference  $P_{phoP}$  promoter, or F1 antigen as claimed would automatically predict the production of a ‘variant’ or fragment’ having the recited promoter or antigenic functions. The specification fails to teach the structure or relevant identifying characteristics of a representative number of promoter ‘variant’ or promoter ‘fragment’, or an F1 ‘variant’ species as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. A skilled artisan cannot envision the detailed chemical structure or morphological properties of a representative number the promoter ‘variant’ or promoter ‘fragment’ species, and F1 ‘variant’ species encompassed by the recited molecules. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is a part of the invention and a reference to a potential method of isolating it. The  $P_{phoP}$  promoter ‘variant’, the  $P_{phoP}$  promoter ‘fragment’ having the promoter activity or the F1 ‘variant’ having the antigenic ability itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

#### **Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)**

9) Claims 1, 2, 11, 15, 22 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a recombinant construct and a recombinant *Salmonella* comprising the construct wherein the construct comprises  $P_{phoP}$  promoter having the nucleotide sequence of SEQ ID NO: 2, operatively interconnected with an isolated nucleic acid that encodes F1 antigen of *Yersinia pestis*, wherein the recombinant *Salmonella* comprising the construct induces an IgA response in a mammal to which it is administered, and a method of expressing the F1 antigen of *Yersinia pestis* using the construct in *Salmonella*, does not reasonably provide enablement for a construct and a recombinant gut-colonizing microorganism comprising the construct wherein the construct comprises  $P_{phoP}$  promoter ‘variants’ or fragments’ operatively interconnected with a nucleic acid that encodes a generic protein, or heterologous protein or an F1 antigenic ‘variant’ of *Yersinia pestis*, wherein the recombinant microorganism

induces protective immune response against a generic ‘organism’ or against *Yersinia pestis* in a mammal to which it is administered, as recited currently. The specification is further not enabled for a method of enhancing expression of a desired protein at mucosal effector sites comprising placing ‘the protein’ under the control of a ‘fragment’ or ‘variant’ of a promoter having SEQ ID NO: 2 and having promoter activity and causing expression in mucosal cells, as recited.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The instant claim 2 is drawn to a construct comprising ‘fragments’ or ‘variants’ of  $P_{phoP}$  promoter operatively interconnected with a nucleic acid encoding a generic protein, i.e., a protein of microbial or non-microbial origin, or a protein of eukaryotic or prokaryotic origin, which is able to induce a protective immune response against a generic ‘organism’ in a mammal to which the construct is administered wherein the construct contains no further elements of the *phoP* gene. While claim 3 is drawn to a recombinant gut-colonizing microorganism transformed with the construct, claim 4 is drawn to the recombinant gut-colonizing microorganism transformed with the construct, which encodes any heterologous protein. Claims 12-14, dependent indirectly from claim 2, are drawn to a vaccine comprising the above-described gut-colonizing microorganism transformed with the construct. Claims 11 and 22 are drawn respectively to a construct and a recombinant gut-colonizing microorganism transformed with the construct wherein the heterologous protein comprises a ‘variant’ of an F1-antigen of *Yersinia pestis*. The  $P_{phoP}$  promoter ‘fragments’ and variants’ are required to have promoter activity, and the ‘variant’ of the F1 antigen of *Yersinia pestis* is required to be antigenic with the ability to induce a protective immune response against *Yersinia pestis* in a mammal to which the recombinant gut-colonizing microorganism containing the construct is administered. A review of the specification indicates a lack of disclosure

of the structure any  $P_{phoP}$  promoter ‘fragments’ and variants’ which retain the promoter activity. This is important because while it is possible to obtain ‘fragments’ and ‘variants’ of a  $P_{phoP}$  promoter, obtaining such ‘fragments’ and ‘variants’ with their promoter activity intact, is not a predictable event. The same is true with the production of biologically functional ‘antigenic variant’ of the F1 antigen of *Yersinia pestis*. The paragraph bridging pages 7 and 8 of the specification states that the antigenic ‘variant’ refers to sequences of amino acids which differ from the base sequence from which they are derived in that one or more amino acids within the sequences are substituted for other amino acids, including conservative and non-conservative amino acids. ‘Variants’ are described herein as having at least 60 to 90% homology with the base sequence. However, no such ‘variants’ of the F1 antigen of *Yersinia pestis* serving as ‘antigenic variants’ while concurrently having the ability to induce a protective immune response in a mammal against *Yersinia pestis* are enabled. Neither the specification nor the art provides guidance as to how to produce an antigenic F1 protein of *Yersinia pestis* having 10 to 40% dissimilarity with the native F1 antigen while retaining the ability to induce a protective immune response in a mammal against *Yersinia pestis*. The instant specification fails to demonstrate that an F1 polypeptide variant having at least 10-40% non-identity to the native F1 antigen, if prepared by one of skill in the art, would retain all the functional, biological or protective properties of the native F1 polypeptide of *Yersinia pestis*. Note that the term ‘vaccine’ ‘must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough’. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

It should further be noted that predictability or unpredictability is one of the *Wands* factors for enablement. The precise structural composition of the recited  $P_{phoP}$  promoter ‘fragments’ and ‘variants’ having the promoter activity, and the precise structure of the F1 antigenic ‘variant’ having the ability to induce a ‘protective’ response in a mammal is not disclosed, without which one of ordinary skill in the art cannot make and use the claimed construct or the recombinant microorganism comprising the construct without undue experimentation. With regard to the F1 ‘variant’, there is no predictability that such a polypeptide variant having as much as 10-40% dissimilarity with the native F1 polypeptide, would remain functional as a protective antigen. This is critical because the art reflects sensitivity of proteins or polypeptides to alteration of even a single

amino acid residue in its amino acid sequence. An alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988) who showed that in the protein, transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that an F1 polypeptide molecule having as much as 10-40% dissimilarity with the native F1 polypeptide, would have its primary, secondary or tertiary structure unchanged and would have the protective ability retained. The effects of such a high dissimilarity upon the polypeptide structure and function are unpredictable. One of skill in the art cannot predict that such a polypeptide variant would have its immunologic or biologic specificity. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein or polypeptide, with as much as 10-40% dissimilarity to the native F1 polypeptide, the protective activity of the recited F1 antigenic variant could not be predicted, based on the sequence identity alone, nor would it be expected to be the same as that of the native F1 polypeptide. For example, if

one nucleotide in the nucleotide sequence that encodes the F1 polypeptide is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native F1 polypeptide. There is no certainty that amino acid substitutions at any position would yield a F1 antigenic 'variant' that retains the protective function and/or the *Y. pestis* specificity of the native F1 polypeptide. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore constructs and recombinant microorganisms encoding such modified molecules are not enabled as Applicants' invention. The specification only discloses a F1 antigenic polypeptide and its expression in a *Salmonella* using the  $P_{phoP}$  promoter of SEQ ID NO: 2. Constructs and recombinant microorganisms encoding undisclosed and unidentified F1 antigenic variant molecules of at least 10-40% identity encompassed in the claims are not enabled for their scope. Although a skilled artisan might envision making a number of changes in the reference F1 polynucleotide sequence and in the  $P_{phoP}$  promoter of SEQ ID NO: 2 in accordance with Applicants' disclosure, it is highly uncertain that the F1 antigenic variant as recited and the promoter 'variants' and 'fragments' as recited would be functionally equivalent to the native F1 polypeptide and the native  $P_{phoP}$  promoter of SEQ ID NO: 2 respectively. The altered F1 polypeptide would vary in an unknown or unpredictable manner from the disclosed native F1 polypeptide. The same is true with an altered  $P_{phoP}$  promoter. For these reasons, making the instantly claimed construct and recombinant organism having the desired function(s) and using the same in the claimed method is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the art, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

### **Rejection(s) under 35 U.S.C § 112, Second Paragraph**

**10)** The following is a quotation of the second paragraph of 35 U.S.C. § 112:  
The specification shall conclude one or more claims particularly pointing out and distinctly claiming the

subject matter which the Applicant regards as his/her invention.

**11)** Claims 1-4, 7-15 and 17-22 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 2 is vague and indefinite in the limitation 'fragments or variants', because it is unclear what is encompassed in this limitation. What constitutes 'fragments or variants', and how much of the promoter's original structure has to be retained such that the resulting products can be considered 'fragments or variants' is not clear. The metes and bounds of the structure encompassed in the limitation 'fragments or variants' are indeterminate.

(b) Claim 1 is vague and indefinite in the limitation 'fragment or variant', because it is unclear what is encompassed in this limitation. What constitutes a 'fragment or variant', and how much of the promoter's original structure has to be retained such that the resulting product can be considered a 'fragment or variant' is not clear. The metes and bounds of the structure encompassed in the limitation 'fragment or variant' are indeterminate.

(c) Analogous criticism applies to claims 11 and 22 with regard to the recitation 'variant'.

(d) Claim 1 is vague in the limitation 'promoter having SEQ ID NO: 2' without distinctly reciting what does SEQ ID NO: 2 represent. Is SEQ ID NO: 2 a nucleotide sequence or an amino acid sequence?

(e) Claim 1 is vague, indefinite, confusing and/or incorrect in the limitation: 'method of expression of a desired protein ..... comprising placing the protein to be expressed under the control of a promoter'. It is unclear how one could enhance the expression of a protein by placing the protein, as opposed to the DNA encoding the protein, under the control of a protein.

(f) Claim 1 is confusing and/or incorrect in the limitation: 'fragment or variant or any of these' because it is unclear what are Applicants trying to convey.

(g) Claim 2 is vague, indefinite and confusing in the limitation: protein, able to induce a protective immune response 'against an organism, in a mammal'. The term 'organism' is broader in scope than the term 'mammal' and includes macroorganism, including humans and animals, as well as microorganisms. It is unclear how a protective immune response against a generic 'organism',

such as a human or animal, can be induced in a mammal by administering to the mammal the claimed construct that encodes a generic protein, such a human or animal protein.

(h) Claim 2 has improper antecedent basis in the limitation: 'the *ompC*, *phoP* or *pagC* gene', because there is no earlier recitation of a *ompC*, *phoP* or *pagC* gene in the claim.

(i) Claims 7 and 19 are indefinite and confusing in the limitation: 'microorganism ... which comprises a *Salmonella* spp.' because it is unclear how a microorganism can 'comprise' within it a *Salmonella* spp.

(j) Claim 10 has improper antecedence in the limitation: construct of claim 2 wherein 'the heterologous protein', because claim 2 does not recite any 'heterologous protein'.

(k) Claim 12 lacks proper antecedent basis in the limitation: 'a recombinant gut-colonising microorganism of claim 3'. For proper antecedence, it is suggested that Applicants replace the limitation with --the recombinant gut-colonising microorganism of claim 3--.

(l) Claim 15 lacks proper antecedent basis in the limitation: 'a recombinant gut-colonising microorganism of claim 3'. For proper antecedence, it is suggested that Applicants replace the limitation with --the recombinant gut-colonising microorganism of claim 3--.

(m) Claim 17 has improper antecedence in the limitation: microorganism of claim 3 wherein 'the heterologous protein', because claim 3 does not recite any 'heterologous protein'.

(n) Claim 20 is incorrect in the limitation: 'promoter has the sequences of SEQ ID NO: ..... or SEQ ID NO: 4' as opposed to the correct limitation --promoter has the sequence of SEQ ID NO: ..... or SEQ ID NO: 4--.

(o) Claim 21 is confusing and/or incorrect in the limitation: '*Salmonella app*' because it is unclear what does 'app' mean.

(p) Claim 22 has improper antecedence in the limitation: microorganism of claim 17 wherein 'the heterologous protein', because claim 3 from which claim 22 indirectly depends, does not recite any 'heterologous protein'.

(q) Claims 3, 4, 7-15 and 17-22, which depend directly or indirectly from claim 2, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

### **Rejection(s) under 35 U.S.C § 102**

**12)** The following is a quotation of the appropriate paragraph(s) of 35 U.S.C. § 102 that form the

basis for the rejection(s) under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in –

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

**13)** Claims 2-4, 7-15, 17-19, 21 and 22 are rejected under 35 U.S.C § 102(e) as being anticipated by Titball *et al.* (US 5,985,285, filed 09/15/1997) ('285).

Titball *et al.* ('285) disclosed a live oral vaccine comprising a pharmaceutically acceptable carrier or an adjuvant and a human or animal gut colonizing microorganism that is transformed with a recombinant DNA construct expressing the heterologous F1 antigen of *Yersinia pestis* under the control of *phoP* *in vivo* inducible promoter (i.e., the  $P_{phoP}$  promoter, a fragment or variant thereof containing no further elements of the *phoP* gene) wherein the DNA is positioned in frame with the promoter. Titball *et al.* ('285) disclosed a method of protecting a human or animal from *Yersinia pestis* infection by administering the live oral vaccine. The vaccine when administered to a human or animal induces local stimulation of the gut-associated lymphoid tissue and stimulates a secretory IgA response by trafficking lymphocytes through the common mucosal immune system (see abstract; claims, particularly claims 44 and 33; Examples; and first full paragraph in column 3). The microorganism is an attenuated *S. typhimurium* or *S. typhi* (see paragraph bridging columns 2 and 3; and first full paragraph in column 3).

Claims 2-4, 7-15, 17-19, 21 and 22 are anticipated by Titball *et al.* ('285).

**14)** Claims 2-4, 7-15, 17-19, 21 and 22 are rejected under 35 U.S.C § 102(b) as being anticipated by Titball *et al.* (WO 96/28551 – Applicants' IDS) ('551).

Titball *et al.* ('551) disclosed a live oral vaccine comprising a pharmaceutically acceptable carrier or an adjuvant and a human or animal gut colonizing microorganism that is transformed with a recombinant DNA construct expressing the heterologous F1 antigen of *Yersinia pestis* under the control of *Phop* *in vivo* inducible promoter (i.e., the  $P_{phoP}$  promoter, a fragment or variant thereof containing no further elements of the *phoP* gene) wherein the DNA is positioned in frame with the promoter. Titball *et al.* ('551) disclosed a method of protecting a human or animal from *Yersinia*

*pestis* infection by administering the live oral vaccine. The vaccine when administered to a human or animal induces local stimulation of the gut-associated lymphoid tissue and stimulates a secretory IgA response by trafficking lymphocytes through the common mucosal immune system (see abstract; claims, particularly claims 46 and 35; Examples; and first full paragraph in column 3). The microorganism is an attenuated *S. typhimurium* or *S. typhi* (see paragraphs 1-3 on page 4).

Claims 2-4, 7-15, 17-19, 21 and 22 are anticipated by Titball *et al.* ('551).

### **Objection(s)**

**15)** Claims 1, 2 and 20 are objected to for including non-elected subject matter.

### **Remarks**

**16)** Claims 1-4, 7-15 and 17-22 stand rejected.

**17)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of after-final amendments is (571) 273-8300.

**18)** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**19)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2005

*SD*  
S. DEVI, PH.D.  
PRIMARY EXAMINER